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Letter to the Editor

The Atrioventricular Canal Defect Is the Congenital Heart Disease Connecting Short Rib-Polydactyly and Oral-Facial-Digital Syndromes

To the Editor:

We read the interesting editorial comment of Neri et al. [1995] pointing out the phenotypic relationship between oral-facial-digital (OFD) and short rib-polydactyly (SRP) syndromes. We agree that a common pathogenetic relation between the two groups does exist. In particular, we think that the study of the anatomic types of congenital heart defects found in both OFD and SRP syndromes may provide further evidence for clinical overlap between the two groups of conditions.

Heart malformations are a cardinal manifestation of the Ellis-van Creveld (EvC) syndrome, the more frequent type being atrioventricular canal defect (AVCD) with common atrium [Lynch et al., 1968; Schinzel, 1983; Marino et al., 1990]. AVC was also reported in the genetic condition signated "single atrium, AVCD-postaxial polydactyly," which is characterized clinically by partial expression of EvC syndrome [Onat, 1994; Digilio et al., 1995a; Levin et al., 1995].

AVCD is the more common heart malformation in patients with Down syndrome [Marino, 1993], and it is frequently found in heterotaxia syndromes [Peoples, 1983]. In addition, our studies have detected a specific association also with monosomy 8p [Marino et al., 1992; Digilio et al., 1993], 3C cranio-cerebello-cardiac syndrome [Digilio et al., 1995b] and Noonan syndrome [Marino et al., 1995]. The specific combination of common atrium and AVCD is rarely diagnosed as isolated malformation in non-syndromic patients. On the contrary, this cardiac defect, frequently with persistent left superior vena cava, is commonly associated with EvC syndrome [Lynch et al., 1968; Schinzel, 1983; Marino et al., 1990] and with heterotaxia syndrome with polysplenia [Peoples, 1983].

Interestingly, the finding of hydrometrocolpos in patients with EvC syndrome [Akoun and Bagard, 1956; Digilio et al., 1996a; Yapar et al., 1996] together with the report of narrow thoracic cage and short limbs in cases with McKusick-Kaufman (MKK) syndrome [Chitayat et al., 1987] suggests the existence of a pathogenetic link between these autosomal recessive conditions. The MKK syndrome is associated with congenital heart defect in 10% of the cases, AVCD or common atrium being described, to the best of our knowledge, in three of the reported cases [McKusick et al., 1964; McKusick, 1978; Pyeritz et al., 1980].

However, the most interesting evidence is emerging from a review of cardiac malformations in OFD syndromes. Although congenital heart defect is not common in this group, a specific association with AVCD has been detected in patients with OFD syndrome type II [Cordero and Holmes, 1977; Iaccarino et al., 1985; Digilio et al., 1996b]. Furthermore, based on the observation of three patients presenting cardiac defects with oral and digital anomalies characteristic of the OFD syndrome type II but without obvious facial component [Örstavik et al., 1992; Digilio et al., 1996b], the existence of an "oro-cardio-digital" variant with AVCD has been suggested [Digilio et al., 1996b].

Interestingly, AVCD is also specifically linked with the hydrolethalus syndrome, since it was diagnosed in half of the reported patients with congenital heart defect [Salonen et al., 1981; Adetoro et al., 1984; Toriello and Bauserman, 1985].

An attempt at reviewing the known reports of oral-facial-skeletal (OFS) syndromes with AVCD is made in Table I. The nonrandom association of AVCD with EvC, OFD type II, hydrolethalus syndromes, and, although less frequently, with other OFS syndromes (Table I) shows that AVCD, with or without common atrium, can represent an additional link between SRP and OFD syndromes.

Clinical variability and genetic heterogeneity of AVCD was demonstrated previously by anatomical and molecular studies [Marino et al., 1990; Wilson et al., 1993; Amati et al., 1995]. Based on the specific association of AVCD with Down and monosomy 8p syndromes, the existence of two "critical regions" for the cardiac defect at chromosome regions 21q22 and 8p23 was suggested [Korenberg et al., 1992; Digilio et al., 1993]. The identification of genes causing oral-facial-skeletal syndromes will likely provide additional candidate loci for genes of AVCD.

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TABLE I. Atrioventricular Canal Defect in Oral-Facial-Skeletal Syndromes*

Syndrome	Cardiac defect	References
Ellis-van Creveld	AVCD, AC	Lynch et al. [1968]
	AVCD, CA	Schinzel [1983]; Marino et al. [1990]; Carmi et al. [1992]
Single atrium AVCD/polydactyly	CA	Onat [1994]
	AVCD, CA	Digilio et al. [1995a]; Levin et al. [1995]
Majewski SRP	AVCD, TA	Majewski et al. [1971]
Kaufman-McKusick	AVCD	McKusick et al. [1964]; Pyeritz and O'Neal Humphries [1980]
	CA	McKusick [1978]
OFD II	AVCD, CA, TA	Cordero and Holmes [1977]
	AVCD	Iaccarino et al. [1985]
	AVCD, AC	Örstavik et al. [1992]
	AVCD, CA	Digilio et al. [1996b]
OFD IIVI	AVCD	Camera et al. [1994]
OFD IV	CA, VSD	Temtamy and McKusick [1978]
OFD VI	AVCD, AC	Gustavson et al. [1971]
Transitional OFD	AVCD	Hingorani et al. [1991]
Pallister-Hall	AVCD	Hall et al. [1980]; Huff and Fernandes [1982]
Hydrolethalus	AVCD	Salonen et al. [1981]; Adetoro et al. [1984]
	AVCD, TrA	Toriello and Bauserman [1985]

* AC, aortic coarctation; AVCD, atrioventricular canal defect; CA, common atrium; OFD, oral-facial-digital; SRP, short rib-polydactyly; TA, truncus arteriosus; TrA, tricuspid atresia; VSD, ventricular septal defect.

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